

(19)



Europäisches Patentamt

European Patent Office

Office européen des brevets



(11)

EP 0 842 660 A1

(12)

EUROPEAN PATENT APPLICATION

(43) Date of publication:

20.05.1998 Bulletin 1998/21

(51) Int. Cl.⁶: **A61K 31/35**, **A61K 35/78**

(21) Application number: 97120182.7

(22) Date of filing: 18.11.1997

(84) Designated Contracting States:

AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC

NL PT SE

Designated Extension States:

AL LT LV MK RO SI

(30) Priority: 18.11.1996 JP 321195/96

(71) Applicants:

• CANCER INSTITUTE (HOSPITAL) CHINESE

ACADAMY OF MEDICAL SCIENCES

Chaoyang District, Beijing 100021 (CN)

• MITSUI NORIN CO., LTD.

Tokyo (JP)

(72) Inventors:

• Cheng, Shu Jun

c/o Cancer Institute (hospital)

Chaoyang District, Beijing 100021 (CN)

• Wang, De Chang

c/o Cancer Institute (hospital)

Chaoyang District, Beijing 100021 (CN)

• Hara, Yukihiko

Fujieda-shi, Shizuoka-ken (CN)

(74) Representative:

VOSSIUS & PARTNER

Siebertstrasse 4

81675 München (DE)

(54) **Composition for treating condyloma acuminata**

(57) The invention describes a pharmaceutical composition containing a tea (*Camellia sinensis*) extract containing catechins (more particularly (-)-epigallocatechin gallate) in the form of a 2-20% by weight ointment or a 50-500 mg tea catechin suppository and its use in the treatment of condyloma acuminata (genital warts) caused by human papilloma virus.

EP 0 842 660 A1

Description

The present invention relates to a composition for treating the hyperplasia caused by papilloma virus, such as condyloma acuminata or genital warts, which contains an extract of tea (e.g. *Camellia sinensis*) containing catechins.

Papilloma viruses are a DNA virus infecting epithelial cells of mammals which cause uncontrolled cell replication. There are many types of papilloma virus infecting human and animal species, but they all can infect the basal epithelial cells and persist in episomal or as DNA integrated into the host genome. The mechanism by which they cause tissue growth may be related to the E4 and E5 proteins they all produce in related forms which appear to interact with p53 and other host proteins which control the cell cycle. The effects of papilloma virus which have been described include genital warts or Condylomata acuminata, common and plantar warts, bovine papillomas, and cervical intra-epithelial neoplasia in women.

According to this method the detection rate is almost 100%. Types HPV6 and 11 of the virus are the ones most commonly detected and because HPV16 has been detected in malignant squamous cell carcinoma from cancer of the penis, cancer of the cervix and Condyloma acuminata, there is a strong possibility that HPV16 is related to the malignancy of Condyloma acuminata.

Means for a treatment of Condyloma acuminata caused by human papilloma virus which have been tried at present are by physical means such as surgical excision, electrocauterization, cryosurgery, laser therapy etc. and medication such as applications of Podophyllin, 5-Fluorouracil, Bleomycin, Interferon, Imiquimod, etc. are presently available. However surgical treatment is distressing for the patient, considering the site of infection, and with topical applications there is the concern of side-effects. These medications work either by cytotoxic tissue destruction or by enhancing the cellular immune response by causing local inflammation. Because of this no conclusive treatment is presently available.

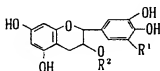
Condyloma acuminata has a high rate of recurrence, and a complete cure is difficult unless treated constantly. Because of this a treatment which has a high degree of safety and is convenient is strongly desired.

Thus for the treatment of condyloma acuminata or other diseases caused by papilloma virus, desired is a treatment which is easy for the patient to take, for example a medication which can be applied to the affected area by the patients themselves showing good results in a relatively short period of use and having no side-effects.

We, the present inventors looked for a natural substance which has no side-effects, may be safely applied for a long period of time by the patients themselves and is notably effective; and after extensive testing we discovered that catechin, a component of tea which is an everyday beverage, is effective and thus the present invention was developed.

Thus the present invention relates to a composition for a treatment of Condyloma acuminata or other diseases caused by papilloma virus containing a tea extract containing catechin as a main component.

The tea catechin used in the present invention is shown below in the general formula 1



wherein R¹ represents H or OH and R² represents H or



The tea catechins are more specifically, epicatechin, epicatechin gallate, epigallocatechin gallate, gallic catechin etc. (including derivatives thereof). These catechins can be used singly or two or more may be mixed together. Out of these it is particularly desirable to have (-)-epigallocatechin gallate as a main component. For example: Polyphenon 100™ (produced by Mitsui Norin Co.; Composition: (+)-gallic catechin 1.44%, (-)-epicatechin 5.81%, (-)-epigallocatechin 17.57%, (-)-epicatechin gallate 12.51%, (-)-epigallocatechin gallate 53.90%) or Polyphenon E™ (produced by Mitsui Norin Co.; Composition: (-)-epicatechin 10.8%, (-)-epigallocatechin 9.2%, (-)-epicatechin gallate 6.5%, (-)-epigallocatechin gallate 54.8%, (-)-gallic catechin gallate 4.0%).

For the treatment of Condyloma acuminata with a composition according to the present invention, the pharmaceutical composition could be used for example in the form of an ointment such as a cream, jelly or emulsion; or in the form

of a suppository such as a capsule, and usually the tea catechin component is combined with an excipient, extending agent, emulsifier, dispersing agent etc. Vaseline is suitable as a base for the ointment. For the ointment the content of tea catechin should be between 2-20% by weight, preferably 5-20% by weight, more preferably between 12-18% by weight, most preferably 15% by weight. In the case of suppository the content of tea catechin should be 50-500mg/capsule, preferably 100-500mg/capsule, more preferably 200-300 capsule, and most preferably 250 mg/capsule.

A typical usage example for the ointment is to apply directly to the infected area of the external genital organs or vagina, a vaseline cream containing 2-20% by weight catechin, from once to several times everyday for a period of 1-2 months. A typical usage example for the suppository in the case where for example the infected area is the cervix or the vagina is to insert a capsule containing 50-500mg tea catechin, from once to several times everyday for a period of 1-2 months.

There is no danger of side-effects from the treatment for condyloma acuminata with the composition of the present invention having tea catechin as the main component thereof since the main component is a natural substance derived from tea which is commonly consumed regularly, and it may be taken for long periods of time. Moreover this medication may be easily applied to or inserted in the infected area by the patients themselves. The composition of the present invention for a treatment of condyloma acuminata has a very high potential for practical use.

Another aspect of the invention is a method of applying tea catechin to an infected area of a patient in an amount which is effective in treating human papilloma virus-infected Condyloma acuminata.

The present invention will be explained in more detail with reference to the following examples which are in no way meant to limit the scope of the invention.

Test Example 1

An ointment consisting essentially of a vaseline based vaginal lubricant containing, as the main component, tea catechin (Trade name: Polyphenon 100, produced by Mitsui Norin Co. Ltd., its main component: (-)-epigallocatechin gallate) was applied to the cervix of healthy mice (50 mice in a group) in catechin dosages of 8mg, 15mg, or 38mg for a period of 7 consecutive days. After this time pathological and histological examinations were carried out and it was determined that except for a mild inflammatory reaction in the cervix of the mice of the 38mg dose group no toxic effect was observed.

Example 1

Clinical tests of the present invention were carried out at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing with a group of 11 women who had been diagnosed with HPV-infected condyloma acuminata. All patients were confirmed to have condyloma in the vulva (external genital organs), and cervix according to clinical examination, cytologic, colposcopic and pathologic tests. Warts were from 0.2 to 2cm in diameter.

Tests were carried out on these 11 patients using either a vaseline-based ointment containing 10 % of tea catechin (Trade name: Polyphenon 100, produced by Mitsui Norin Co. Ltd., crude catechin content is about 90% and its main component is (-)-epigallocatechin gallate) or using a suppository containing 300mg/capsule of the above tea catechin. Applying the ointment to the external genital organs and applying the suppository to the cervix, the treatments of the present invention were used continuously once a day for about two months.

During the period of treatment examinations and colposcopic tests of the infected areas were carried out. Results obtained are shown in Table 1. As shown in the table, when the infected area completely disappeared it was judged to be cured, when 50% or more disappeared it was judged to be improved and when less than 50% or nothing disappeared it was judged there was no effect.

Table 1

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	9	4	3	2
Cervix	2	1	0	1

As is evident from the table, 7 cases out of 9 (77.8%) of condyloma acuminata of the external genital organ showed a clear effect (being either cured or improved). In one case of the cervical infection the tumor completely disappeared, thus cured. During this period, apart from some patients who experienced slight pain or inflammation in the infected area and a few other patients who felt some itching, there were no obvious side-effects observed.

Example 2

The clinical tests at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing were conducted in the same manner as in Example 1 using a vaseline-based ointment containing 15% tea catechin as above or external and internal warts with a group of 33 female patients diagnosed with HPV-infected condyloma acuminata. In this group, 8 of the patients were infected in two areas. Results are shown in Table 2. As is evident from the table, 92% of condyloma acuminata of the external genital organs and 70% of the vaginal condyloma acuminata was cured or improved, and in the case of the cervical condyloma acuminata, all cases were cured, 25 cases out of 41 cases showed the result as cured and the curing ratio was 61%.

Table 2

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	26	18	6	2
Vagina	10	2	5	3
Cervix	5	5	0	0
Total (%)	41	25 (61.0)	11 (26.8)	5 (12.2)

Example 3

The clinical test at the Cancer Institute, Chinese Academy of Medical Sciences in Beijing was conducted in the same manner as in Example 2 except the ointment contained 15% of a different tea extract (PolyphenonE, produced by Mitsui Norin Co., Ltd., similar to Polyphenon 100, crude catechin content is about 82% and its main component is (-)-epigallocatechin gallate), with a group of 22 female patient diagnosed with HPV-infected condyloma acuminata. Results are shown in Table 3. As is evident from the table, out of 16 cases of condyloma acuminata of the external genital organs 7 were cured and 6 improved; a total of 13 (81.3%) being effected. In the case of condyloma acuminata of the vagina, out of 6 cases 3 were cured and 2 were improved; a total of 83.3% was confirmed to be effected.

Table 3

Infected Area	No. of Patients	Cured	Improved	No Effect
External genital organs	16	7	6	3
Vagina	6	3	2	1
Total (%)	22	10 (45.5)	8 (36.4)	4 (18.2)

The entire disclosure of Japanese Patent Application No. 8-321195 filed on November 18, 1996 including specification, claims and summary are incorporated herein by reference in its entirety.

Claims

1. A pharmaceutical composition for the treatment of papilloma virus-infected tissue which comprises tea extract containing catechin or a derivative thereof as the effective ingredient.
2. The composition according to claim 1 wherein the tea extract contains (-)-epigallocatechin gallate or a derivative thereof as a main component.
3. The composition according to claim 1 or 2, wherein said composition is in the form of an ointment.
4. The composition according to claim 1 or 2, wherein said composition is in the form of a suppository.
5. The composition according to claim 1 or 2, wherein said composition is in the form of a specialized delivery system to reach the infected tissue with the tea extract.

EP 0 842 660 A1

6. The composition according to claim 3 wherein said onitment contains 2-20% by weight of crude catechin of tea extract containing catechin.
7. The composition according to claim 4 wherein said suppository contains 50-500mg by weight of crude catechin of tea extract containing catechin.
8. Use of tea extract containing catechin for the preparation of a pharmaceutical composition according to claim 1 or 2 for the treatment of tissue hyperplasia caused by papilloma virus, such as genital warts.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 12 0182

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	US 5 135 957 A (TADAKATSU SHIMAMURA) * column 2 line 28, lines 53-59 *	1-3,6	A61K31/35 A61K35/78
X	GB 2 293 548 A (J.L. HIBBERT) * abstract * * page 2, line 20 - line 34 * * page 3 lines 13-20, 26-31 * page 4, line 15 - line 24 *	1,3,5	
X	DATABASE WPI Week 9130 Derwent Publications Ltd., London, GB; AN 91-219271 XP002054466 & JP 03 141 220 A (TSUMURA & CO), 17 June 1991 * abstract *	1,2,4,7	
X	DE 22 06 570 A (ZYMA S.A.) * page 2 point b) * * examples 4,5 * * claim 4 *	1,4,7	
X	WO 96 28178 A (INDENA S.P.A.) * claims 14,15,20,21 * * page 8 - page 9 * * page 5, line 13 - line 23 *	1,2,4	
X	EP 0 417 385 A (MITSUI NORIN CO LTD) * the whole document *	1	
-/--			
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 4 February 1998	Examiner Gac, G
CATEGORY OF CITED DOCUMENTS		T theory or principle underlying the invention E earlier patent document, but published on, or after the filing date D document cited in the application L document cited for other reasons S member of the same patent family, corresponding document	
X particularly relevant if taken alone Y particularly relevant if combined with another document of the same category A technological background O non-written disclosure P intermediate document			

EPO FORM 1503 (02/92) (PCT/91)



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 12 0182

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
X	STICH ET AL.: "The effect of retinoids, carotenoids and phenolics on chromosomal instability of bovine papillomavirus DNA-carrying cells" MUTAT. RES., vol. 241, no. 4, 1990, pages 387-393, XP002054463 * the whole document, especially page 392, left column at the bottom *	8	
A	MUHKAR ET AL.: "Green tea and skin-anticarcinogenic Effects" J. INVEST. DERMATOL., vol. 102, no. 1, 1994, pages 3-7, XP002054464 * the whole document *	1-3.8	
A	HIROSE ET AL.: "Inhibition of mammary gland carcinogenesis by green tea catechins and other naturally occurring antioxidants in female Sprague-Dawley rats pretreated with 7,12-dimethylbenz[a]anthracene" CANCER LETT., vol. 83, no. 1-2, 1994, pages 149-156, XP002054465 * the whole document *	8	TECHNICAL FIELDS SEARCHED (Int.Cl.6)
A	DE 42 11 238 A (BUDOWSKI) * page 2 lines 7, 31-38 *	8	
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 4 February 1998	Examiner Gac, G
CATEGORY OF CITED DOCUMENTS X: particularly relevant if taken alone Y: particularly relevant if combined with another document of the same category A: technological background O: non-written disclosure P: intermediate documents T: theory or principle underlying the invention E: earlier patent document but published on or after the filing date O: document cited in the application L: document cited for other reasons & member of the same patent family, corresponding document			